

Does Body Mass Index Influence the Outcomes After Surgery for Locally Advanced Prostate Cancer?

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Abstract: *Introduction:* A higher body mass index (BMI) has been correlated with worse outcome after radical prostatectomy (RP), but this observation has been mainly noticed in clinically localized disease. The objective of this study is to analyze the relationship between BMI and outcome of surgery for clinical unilateral T3a (cT3a) prostate cancer.

Patients and Methods: Two hundred patients with cT3a prostate cancer underwent RP between 1987 and 2004. The BMI of each patient was recorded before surgery. Patients were divided into 2 groups: BMI <25 and ≥25. The Cox proportional hazard analysis was used to study the differences in outcome between these two groups.

Results: The mean age was 63.3 years (range 41 to 79). The mean follow-up was 70.6 months (range 7 to 177). Ninety-three patients had BMI <25, and 107 patients had BMI ≥25. There were no significant differences between BMI <25 and ≥25 in the incidence of node positive disease (p=0.22) and margin status (p=0.48). Neither were there significant differences between these two groups in pre-operative PSA (p=0.15) and cancer volume (p=0.07). In the Cox proportional hazard analysis, BMI was a significant predictor in clinical progression free survival (CPFS).

Conclusion: BMI has been correlated with worse outcome after RP in clinically localized disease. We could confirm this observation in CPFS of cT3a disease. However, while oncological outcomes seem to differ, this type of surgery may be very demanding and postoperative short-term morbidity may also be higher in patients with BMI ≥25.

Key Words: Body mass index, cT3, prostate cancer.

INTRODUCTION

Body mass index (BMI) (also called the “Quetelet index”) was invented by a Belgian mathematician Lambert Adolphe Quetelet in 19th century. Now it is the most widely used tool to measure the status of obesity. BMI is defined as the body weight divided by square of height, with overweight defined as an index of more than 25.

In a large cohort study of 950000 Norwegian men followed for an average of 21 years, Engeland *et al.* found that the effect of BMI on the incidence of prostate cancer was modest [1]. Bradbury *et al.* found that obese men (BMI ≥30) were at lower risk of developing prostate cancer compared to normal weight men [2]. Giovannucci *et al.* agreed on this point, they considered that the risk of prostate cancer in men with a higher BMI (≥ 30) was lower than in men with a lower BMI (23-24.9) but only if they were younger (<60 years old) [3]. This was also shown by Porter *et al.*, who found that men with a BMI >29 had the lowest risk of prostate cancer. They concluded that obesity is inversely related to prostate cancer risk in middle-aged (40-64 years old) men [4]. Recently studies by Kurahashi *et al.* and Baillargeon *et al.*, both of them described that BMI was not significantly associated with risk of prostate cancer [5,6]. Presti *et al.* categorized BMI of 787 patients into 3 groups (normal: <25, overweight: 25-29.9 and obese: >30), they found detection rates of prostate cancer were highest in the normal group

(52%) compared to overweight (37%) and obese (42%) [7]. A more detailed analysis was performed by Kobayashi *et al.*, who stratified 481 men with TRUS biopsy into 3 BMI groups (BMI <23, 23-25, >25). Similar to the result by Presti *et al.*, they found no significant differences between cancer detection rate and BMI groups on univariate analysis, but there was a significant association between BMI and cancer detection on multivariate analysis. They concluded that BMI had a significant impact on prostate cancer detection rate [8].

BMI might correlate with worse outcome after radical prostatectomy (RP), but this observation has been mainly noticed in clinically localized disease. The objective of this study is to investigate the correlation between BMI and outcomes of surgery for locally advanced prostate cancer in a single center series.

PATIENTS AND METHODS

Population of Patients

Between 1987 and 2004, 235 patients with clinical unilateral T3a prostate cancer detected by digital rectal examination (DRE) underwent RP and bilateral pelvic lymphadenectomy at our institution. Thirty-five patients who received neoadjuvant treatment before surgery were excluded. Two hundred patients were included in the final analysis. They were selected for operation on the basis of limited, unilateral cT3a, any Gleason score, any PSA and Eastern Cooperative Oncology Group (ECOG) performance status 0-1. All patients had negative finding on both contrast enhanced computed tomography of the pelvis and bone scan.

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The patients were categorized into 2 subgroups according to the BMI at surgery: <25 and ≥ 25 .

The last serum PSA value obtained prior to prostate biopsies was used in the analysis. Surgery was performed by one of 2 senior surgeons according to the technique as previously described [9]. The pathological reports were recorded, and lymph node status was assigned, based on the 2002 TNM classification [10]. Status of surgical margin and cancer volume were also recorded.

Biochemical progression was defined as any serum PSA ≥ 0.2 ng/ml, clinical progression was defined as local recurrence or distant metastasis according to previous description [11]. Local recurrence was defined as the presence of cancer cells at the pelvic area proven by pathological examination. Distant metastasis was defined as tumor detected by bone scan, CT or MRI outside the pelvic area. Cancer-specific survival (CSS) was defined as the time from RP to death due to prostate cancer or complications of this disease. Overall survival (OS) was defined as the time from RP to death by any cause.

Statistical Analysis

All categorical variables (nodal status, margin and pathological stage) were analyzed by chi-square analysis or Fisher's exact test, continuous variables (age, preoperative PSA and cancer volume) were compared by one-way analysis of variance or Mann-Whitney test. The Cox proportional hazard analysis was used to determine the prognostic indicators of disease progression. The Kaplan-Meier method was used to analyse biochemical progression free survival (BPFS) and clinical progression free survival (CPFS), CSS and OS. The differences between subgroups were tested by log-rank test. MedCalc® statistical software, version 8.1.0.0 (MedCalc Software, Belgium) and SPSS v12.0 were used for the analysis.

RESULTS

Ninety-three patients had BMI <25 , and 107 patients had BMI ≥ 25 . The patient's characteristics and pathological findings were listed in Table 1. The mean age was 63.3 years (range 41 to 79). The mean follow-up was 70.6 months (range 7 to 177). The average preoperative PSA was 14.9 ng/ml (range 1.0-127.0). Forty-seven patients (23.5%) were confirmed with organ confined disease (pT2), 145 (72.5%) were pT3 including 113 (56.5%) with extraprostatic extension only and 32 (16%) with seminal vesicle invasion. Eight patients (4%) had adjacent structure invasion (pT4). Seventeen patients (8.5%) were found with lymph node involvement, 67 patients (33.5%) had positive surgical margin. Both median biopsy and surgical Gleason score were 7. One hundred twelve patients (56%) received adjuvant or salvage treatment (ADT, RT or both) after RP. Local recurrence was found in 4 patients, distant metastasis was found in 13 patients. Seven patients died of prostate cancer, 15 patients died of other causes.

There were no significant differences between BMI <25 and ≥ 25 in the incidence of positive pelvic lymph node ($p=0.22$) and positive surgical margin ($p=0.48$). Neither were there significant differences between these two groups in age ($p=0.84$), pre-operative PSA ($p=0.15$), cancer volume ($p=0.07$), surgical Gleason score ($p=0.17$) and pathological stage ($p=0.49$) (Table 1).

In patients with BMI <25 , margin status, pathological stage and preoperative PSA were significant predictors in BPFS on univariate analysis; however margin status was the only significant predictor on multivariate analysis (Table 2). In patients with BMI ≥ 25 , except Gleason score all the parameters were significant predictors in BPFS on univariate analysis; margin and node status were significant predictors on multivariate analysis (Table 3).

In all, on Cox multivariate analyses, BMI and surgical Gleason score were independent predictive factors in CPFS.

Table 1. The Patient's Characteristics

BMI	<25	≥ 25	p Value
Patient number	93	107	
Mean age (range)	63.5 (43-79)	63.1 (41-76)	0.839
Mean PSA ng/ml (range)	13.32 (1.00-57.92)	16.23 (1.20-127.00)	0.153
Positive node (n, %)	5 (5.4%)	12 (11.2%)	0.222
Positive margin (n, %)	34 (36.6%)	33 (30.8%)	0.481
Mean cancer volume (ml) (range)	5.69 (0.25-27.70)	7.73 (0.20-31.00)	0.074
Median surgical Gleason score (range)	7 (5-9)	7 (4-9)	0.168
Pathological stage (n, %)			
T2	24 (25.8%)	23 (21.5%)	0.494
T3a	54 (58.1%)	59 (55.1%)	
T3b	13 (14.0%)	19 (17.8%)	
T4	2 (2.2%)	6 (5.6%)	

Table 2. The Cox Proportional Univariate and Multivariate Analyses of Biochemical Progression Free Survival (BPFS) in 93 Patients with BMI <25

Parameters	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	P value	HR	95% CI	P value
Cancer Volume	1.027	0.975-1.081	0.320	0.979	0.916-1.046	0.524
Gleason score	1.060	0.751-1.498	0.741	1.063	0.740-1.528	0.741
Margin	3.302	1.667-6.538	<0.001	2.337	1.069-5.110	0.034
Node	1.768	0.544-5.744	0.346	0.736	0.191-2.837	0.657
Pathological stage	1.663	1.036-2.669	0.036	1.519	0.821-2.812	0.185
Preoperative PSA	1.036	1.011-1.061	0.004	1.028	0.998-1.059	0.067

Table 3. The Cox Proportional Univariate and Multivariate Analyses of Biochemical Progression Free Survival (BPFS) in 107 Patients with BMI ≥25

Parameters	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	P value	HR	95% CI	P value
Cancer Volume	1.079	1.035-1.124	<0.001	1.050	0.999-1.104	0.055
Gleason score	1.031	0.768-1.385	0.839	0.801	0.589-1.090	0.161
Margin	3.733	2.047-6.806	<0.001	2.884	1.525-5.453	0.001
Node	3.837	1.826-8.063	<0.001	2.587	1.170-5.721	0.020
Pathological stage	2.399	1.620-3.553	<0.001	1.572	0.949-2.603	0.081
Preoperative PSA	1.016	1.003-1.030	0.021	1.002	0.983-1.020	0.870

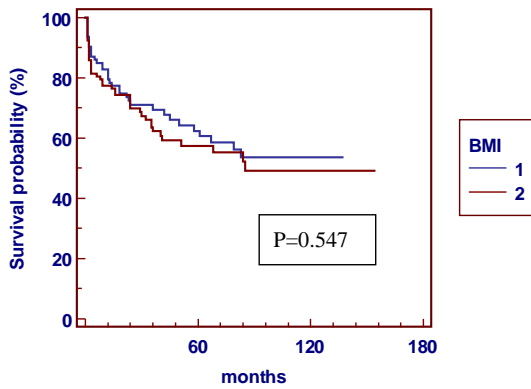
Table 4. The Multivariate Analyses in BPFS, CPFS and OS

Covariates	BPFS			CPFS			OS		
	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p
Preoperative PSA	1.02	1.01-1.04	<0.01	0.95	0.88-1.02	0.13	1.01	0.99-1.03	0.40
Surgical Gleason score	1.17	0.65-2.10	0.59	0.16	0.03-0.89	0.04	0.64	0.25-1.65	0.36
Pathological stage	0.53	0.22-1.29	0.16	3.17	0.37-27.15	0.29	0.61	0.13-2.84	0.53
Node	0.81	0.36-1.79	0.69	0.99	0.10-10.34	0.99	0.57	0.17-1.86	0.35
Margin	1.15	0.63-2.09	0.66	2.76	0.42-18.38	0.29	0.66	0.24-1.88	0.44
Cancer volume	1.02	0.98-1.06	0.44	1.06	0.96-1.16	0.29	1.08	1.01-1.15	0.02
BMI	0.99	0.92-1.06	0.71	1.93	1.23-3.02	<0.01	1.01	0.86-1.17	0.98

Preoperative PSA was an independent predictor in BPFS. Cancer volume was an independent factor in OS (Table 4). In Kaplan-Meier analysis, there was a significant difference between BMI <25 and ≥25 in OS ($p=0.547$ in BPFS, 0.052 in CPFS, 0.229 in CSS and 0.045 in OS) (Fig. 1A, 1B, 1C,

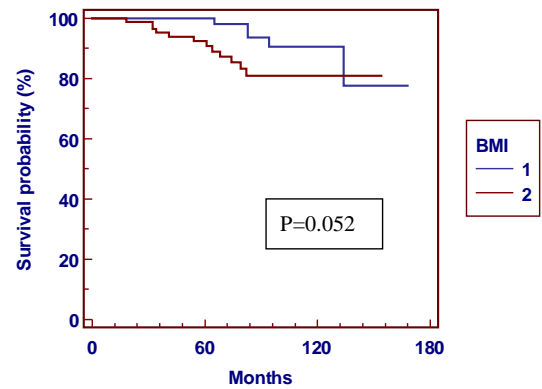
1D). At 5 years, BPFS was 62.4% in the group with BMI <25 and 57.4% in the group with BMI ≥25, CPFS was 100% and 92.4%, CSS was 100% and 97.5%, and OS was 98.7% and 93.4% respectively.

1A



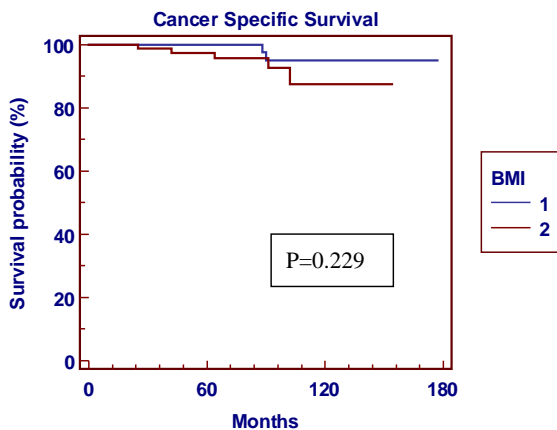
Months	0	60	120	180
Patients at risk (BPFS) BMI <25	93	34	5	0
BMI ≥25	107	30	1	1

1B



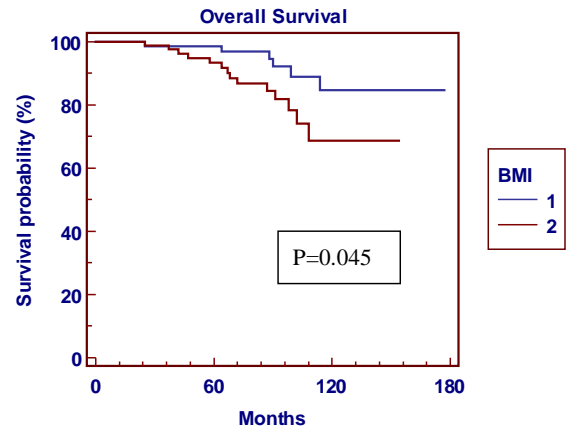
Months	0	60	120	180
Patients at risk (CPFS) BMI <25	93	60	15	1
BMI ≥25	107	57	5	0

1C



Months	0	60	120	180
Patients at risk (CSS) BMI <25	93	60	16	1
BMI ≥25	107	61	7	0

1D



Months	0	60	120	180
Patients at risk (OS) BMI <25	93	60	16	1
BMI ≥25	107	61	7	0

Fig. (1). The survival outcomes between BMI <25 and BMI ≥25 (1: BMI <25, 2: BMI ≥25).

DISCUSSION

Obesity has been a problem in western countries for a long time. In this article, we compared the outcomes of the patients with BMI <25 and ≥25 in locally advanced T3a prostate cancer. Margin status was proved a predictive factor in BPFS, either BMI <25 or ≥25. For the patients with BMI ≥25, node status should be noted.

BMI and Surgical Margin

Obesity has been associated with higher incidence of positive surgical margins, [12,13]. A recently report by Magheli *et al.*, 5631 patients were enrolled in this study, concluded that lower BMI was significantly associated with lower rates of positive surgical margin [14]. For locally advanced prostate cancer, although there was no significant

difference in status of margin between BMI<25 and ≥25, we proved status of surgical margin was an independent predictive factor in BPFS either in BMI<25 and ≥25. A positive surgical margin was found in 67 patients (33.5%). When we analysed the evolution of positive surgical margins in time, the positive margin rates improved dramatically from 66.7% in the period 1987-1994 to 43.3% in the period 1995-1999 to 10.0% in the period 2000-2004. It was clear that margin rate was improved with gaining more experience in surgery for cT3 prostate cancer.

BMI and Risk of High-Grade Prostate Cancer

Baillargeon *et al.* reported that BMI was not associated with either high-grade or low-grade disease [6]. Contradictory opinions were reported by several authors. In a large

series of 2952 prostate cancer patients with complete BMI information from CaPSURE (Cancer of the Prostate Strategic Urologic Research Endeavor), Kane *et al.* found that increased obesity was associated with a slightly increased chance of having high risk prostate cancer at diagnosis [15]. At the same time, Freedland *et al.* reported that a higher BMI was positively associated with being diagnosed with prostate cancer. They also found that a higher BMI increased the odds of high-grade disease in men with prostate cancer [16]. Gong *et al.* examined the relationship between obesity and the risk of low- or high-grade prostate cancer. They reported that compared with men with BMI <25, obese men (BMI ≥ 30) had an 18% decreased risk of low-grade (Gleason <7) prostate cancer and a 29% increased risk of high-grade prostate cancer (Gleason ≥ 7) or a 78% increased risk of Gleason score 8 to 10. They concluded that obesity increases the risk of high-grade but decreases the risk of low-grade prostate cancer [17]. In current study, for cT3a prostate cancer, there was no significant difference in surgical Gleason score between the patients with BMI <25 and ≥ 25 . Surgical Gleason score was not a predictor of BPFs. However, surgical Gleason score was an independent predictive factor in CPFS on multivariate analyses.

BMI and Biochemical Progression After RP

Strom *et al.* described that patients with BMI ≥ 30 had a higher rate of biochemical failure compared with non-obese men. They reported that a higher BMI was a significant independent predictor for biochemical progression after RP in multivariate analysis [18]. This opinion was shared by Bassett *et al.* who reported that the patients with a BMI ≥ 35 were 1.69 times more at risk to experience biochemical failure than patients with normal weight (BMI <25). They considered that increasing BMI was significantly associated with biochemical progression [19]. A recently study by Hisasue *et al.*, proved BMI to be an independent predictor for PSA recurrence on the multivariate analysis [20]. Freedland *et al.* reported that increasing BMI was associated with increasing odds of capsular incision. They found that mild obesity was associated with a 30% increase in odds of capsular incision, while moderate and severe obesity was associated with 57% increasing odds of capsular incision compared to normal weight patients [21]. The technique of retropubic RP is more difficult in obese patients. They also reported that increasing BMI was associated with high grade disease in the RP specimen, positive surgical margins, extra-prostatic extension, lymph node metastasis and also increasing risk of biochemical progression [22]. These data showed obesity can influence the outcome after RP.

Several studies showed that a higher BMI correlates with a higher risk of biochemical progression in localized prostate cancer. However, in clinical unilateral T3a prostate cancer, we found BMI was not a predictor in BPFs and OS, but it was a significant predictor in CPFS.

In the current study, Kaplan –Meier analysis showed no significant differences for CPFS while Cox analysis did show significant differences. Because Cox analysis is a multivariate analysis, p value may difference from Kaplan –Meier analysis which is a uni-variate analysis.

The limitations of this study: the small number of patients. Not all clinical T3 cases agreed to undergo RP, they had the choice between RT or ADT. Most of our patients were Caucasians. Because of these limitations, further study may be required.

CONCLUSION

BMI has been correlated with worse outcome after RP in clinically localized disease. We could confirm this observation in CPFS of cT3a disease. Furthermore, besides the fact that oncological outcomes differ, this type of surgery may also be very demanding and postoperative short-term morbidity may also be higher in patients with BMI ≥ 25 .

REFERENCES

- [1] Engeland A, Tretli S, Bjorge T. Height, body mass index, and prostate cancer: a follow-up of 950000 Norwegian men. *Br J Cancer* 2003; 89(7): 1237-42.
- [2] Bradbury BD, Wilk JB, Kaye JA. Obesity and the risk of prostate cancer (United States). *Cancer Causes Control* 2005; 16(6): 637-41.
- [3] Giovannucci E, Rimm EB, Liu Y, *et al.* Body mass index and risk of prostate cancer in U.S. health professionals. *J Natl Cancer Inst* 2003; 95(16): 1240-4.
- [4] Porter MP, Stanford JL. Obesity and the risk of prostate cancer. *Prostate* 2005; 62(4): 316-21.
- [5] Kurahashi N, Iwasaki M, Sasazuki S, Otani T, Inoue M, Tsugane S. Association of body mass index and height with risk of prostate cancer among middle-aged Japanese men. *Br J Cancer* 2006; 94(5): 740-2.
- [6] Baillargeon J, Platz EA, Rose DP, *et al.* Obesity, adipokines, and prostate cancer in a prospective population-based study. *Cancer Epidemiol Biomarkers Prev* 2006; 15(7): 1331-5.
- [7] Presti JC Jr, Lee U, Brooks JD, Terris MK. Lower body mass index is associated with a higher prostate cancer detection rate and less favorable pathological features in a biopsy population. *J Urol* 2004; 171(6 Pt 1): 2199-202.
- [8] Kobayashi T, Mitsumori K, Nishizawa K, Kawahara T, Ogura K, Ide Y. Association between body mass index and prostate cancer detection rates in Japanese urologic patients. *Urology* 2005; 66(1): 130-4.
- [9] Hsu CY, Joniau S, Van Poppel H. Radical prostatectomy for locally advanced prostate cancer; technical aspects of radical prostatectomy. *EAU Update Series* 2005; 3: 90-7.
- [10] Sobin LH, Wittekind C. *TNM Classification of prostate cancer*. 6th ed. Wiley-Liss: New York 2002; pp. 184-7.
- [11] Hsu CY, Joniau S, Oyen R, Roskams T, Van Poppel H. Outcome for clinical unilateral T3a prostate cancer; a single-institution experience. *Eur Urol* 2007; 51(1): 121-9.
- [12] Herman MP, Raman JD, Dong S, Samadi D, Scherr DS. Increasing body mass index negatively impacts outcomes following robotic radical prostatectomy. *JSL* 2007; 11(4): 438-42.
- [13] Castle EP, Atug F, Woods M, Thomas R, Davis R. Impact of body mass index on outcomes after robot assisted radical prostatectomy. *World J Urol* 2008; 26(1): 91-5.
- [14] Magheli A, Rais-Bahrami S, Trock BJ, *et al.* Impact of body mass index on biochemical recurrence rates after radical prostatectomy; An analysis utilizing propensity score matching. *Urology* 2008; 72(6): 1246-51.
- [15] Kane CJ, Bassett WW, Sadetsky N, *et al.* Obesity and prostate cancer clinical risk factors at presentation; data from CaPSURE. *J Urol* 2005; 173(3): 732-6.
- [16] Freedland SJ, Terris MK, Platz EA, Presti JC Jr. Body mass index as a predictor of prostate cancer; development versus detection on biopsy. *Urology* 2005; 66(1): 108-13.
- [17] Gong Z, Heuvelink ML, Goodman PJ, *et al.* Obesity diabetes, and risk of prostate cancer; results from the prostate cancer prevention trial. *Cancer Epidemiol Biomarkers Prev* 2006; 15(10): 1977-83.
- [18] Strom SS, Wang X, Pettaway CA, *et al.* Obesity, weight gain, and risk of biochemical failure among prostate cancer patients following prostatectomy. *Clin Cancer Res* 2005; 11(19 Pt 1): 6889-94.

- [19] Bassett WW, Cooperberg MR, Sadetsky N, *et al.* Impact of obesity on prostate cancer recurrence after radical prostatectomy; data from CaPSURE. *Urology* 2005; 66(5): 1060-5.
- [20] Hisasue S, Yanase M, Shindo T, *et al.* Influence of body mass index and total testosterone level on biochemical recurrence following radical prostatectomy. *Jpn J Clin Oncol* 2008; 38(2): 129-33.
- [21] Freedland SJ, Grubb KA, Yiu SK, *et al.* Obesity and capsular incision at the time of open retropubic radical prostatectomy. *J Urol* 2005; 174: 1798-801.
- [22] Freedland SJ, Grubb KA, Yiu SK, *et al.* Obesity and risk of biochemical progression following radical prostatectomy at a tertiary care referral center. *J Urol* 2005; 174: 919-22.

Received: October 16, 2008

Revised: January 14, 2009

Accepted: January 20, 2009

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